Joint Effects between UDP-Glucuronosyltransferase 1A7 Genotype and Dietary Carcinogen Exposure on Risk of Colon Cancer

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Abstract

The UDP-glucuronosyltransferase 1A7 (*UGT1A7*) gene is polymorphic and encodes an enzyme involved in the detoxification of heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH). Consumption of pan-fried and well-done meat are surrogates for HCA and PAH exposure and are possibly associated with colon cancer. We have evaluated whether *UGT1A7* allelic variations are associated with colon cancer and whether *UGT1A7* genotype modified associations among meat intake, exposure to HCAs and PAHs, and colon cancer in a population-based case-control study of African Americans (197 cases and 202 controls) and whites (203 cases and 210 controls). As part of a 150-item food frequency questionnaire, meat intake was assessed by cooking method and doneness and used to estimate individual HCA and PAH exposure. *UGT1A7* alleles (*UGT1A7*1*, *UGT1A7*2*, *UGT1A7*3*, and *UGT1A7*4*) were measured and genotypes were categorized into predicted activity groups (high: *1/*1, *1/*2, *2/*2; intermediate: *1/*3, *1/*4, *2/*3; low: *3/*3, *3/*4, *4/*4). There was no association with *UGT1A7* low versus high/intermediate genotype [odds ratio (OR), 1.1; 95% confidence interval (95% CI), 0.7-1.8], regardless of race. Greater than additive joint effects were observed for *UGT1A7* low genotype and HCA-related factors. For example, equal to or greater than the median daily intake of the HCA, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) and having *UGT1A7* low genotype was positively associated with colon cancer (OR, 2.4; 95% CI, 1.2-4.8), compared with less than the median daily intake and *UGT1A7* high/intermediate genotypes. These data suggest that the associations among cooked meat–derived compound exposure, and colon cancer are modified by the *UGT1A7* genotype. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1626–32)

Introduction

Heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) are known mutagens and possible human carcinogens (1-3) formed in meat while it is cooked and are most concentrated on the meat surface. The optimal conditions for HCA formation include high-temperature cooking such as pan-frying and grilling (4-6). Meat that is cooked above a heat source, by methods such as grilling or barbecuing, contain the highest levels of PAHs because the meat is exposed to smoke formed from the pyrolysis of fatty juices that drip down onto the heat source (7). Consumption of pan-fried, grilled, or barbecued well-done meat are surrogates for HCA and PAH exposure and may be positively associated with colon cancer (8).

UDP-glucuronosyltransferases (UGT) are a family of enzymes that catalyze the glucuronidation of both endogenous compounds, such as bilirubin and steroid hormones, as well as exogenous compounds, such as environmental carcinogens and dietary constituents (9). Glucuronidation is a primary route of detoxification of the HCA, 2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine (PhIP) and its carcinogenic intermediate 2-hydroxyamino-1-methyl-6-phenylimidazo[4,5-b]pyridine (*N*-OH-PhIP; refs. 10-12). Results from a human exposure study identified N^2-OH-PhIP-N^2-glucuronide as the predominant urinary metabolite (13), suggesting that a large proportion of ingested PhIP is converted into *N*-OH-PhIP and subsequently conjugated with glucuronic acid by UGTs (14, 15). In contrast, the extent of the *in vivo* role of the glucuronidation pathway for other HCAs, such as 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) remains to be shown but most likely involved UGT1A enzyme family (16). *In vitro* evidence is present for the glucuronidation of the PAH, benzo(a)pyrene, and its hydroxylated derivatives, resulting in the detoxification of these compounds (17, 18).

The polymorphic isozyme UGT1A7 has been specifically implicated in the glucuronidation of HCAs (19, 20) and benzo(a)pyrene (21, 22). The *UGT1A7*3* and *UGT1A7*4* alleles have shown a lower catalytic activity towards a number of substrates including PhIP and the 3-hydroxy-benzo(a)pyrene, 7-hydroxy-benzo(a)pyrene, and 9-hydroxy-benzo(a)pyrene derivatives, suggesting that these variants confer a slow glucuronidation phenotype (19, 21). In addition, localization of glucuronidation throughout the digestive tract provides strong etiologic evidence for its role in HCA and benzo(a)-pyrene-mediated carcinogenesis in the gut (23, 24).

Few epidemiologic studies have examined *UGT1A7* alleles in relation to cancer. The presence of the *UGT1A7*3* allele was

Received 9/16/04; revised 4/22/05; accepted 4/27/05.

Grant support: Center for Environmental Health and Susceptibility grant NIEHS P30-ES10126 (R.C. Millikan), Lineberger Comprehensive Cancer Center core grant P30-CA16086 (R.C. Millikan), NIH grants RO1-CA 66635 and P30 DK 34987 (R.S. Sandler), Canadian Institutes of Health Research grant 177282 (C. Guillemette), the Canada Research Chair Program (C. Guillemette), Canadian Institutes of Health Research studentship award (Y. Duguay), and Canada's Research-Based Pharmaceutical Companies (Y. Duguay).

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reported to have an almost 3-fold association [odds ratio (OR), 2.8; 95% confidence interval (95% CI), 1.6-4.7] with colorectal cancer compared with the wild-type *UGT1A7*1* allele (19). However, this case-control study was relatively small and hospital-based. Given the biological plausibility for the role of UGTs in the etiology of colon cancer, a larger epidemiologic study conducted in a population-based sample with relevant UGT substrate exposure information is needed to more fully explore whether *UGT1A7* polymorphisms are associated with colon cancer.

We recently reported modest positive associations with increasing intake for well-done and pan-fried red meat, and the HCA, DiMeIQx from the North Carolina Colon Cancer Study, a population-based, case-control study of African Americans and whites (8). In the analyses presented here, we have evaluated the hypothesis that lower *UGT1A7* predicted activity genotypes are associated with an increased risk of colon cancer and that lower UGT1A7 activity results in greater susceptibility to dietary sources of HCA and benzo(a)pyrene exposure on risk of colon cancer.

Materials and Methods

Study Population. Cases and controls of the North Carolina Colon Cancer Study were selected from 33 counties in North Carolina and frequency matched to cases by race, age, and sex (25). Cases were selected through a rapid ascertainment system (26) and were eligible if they were between 40 and 80 years of age at first primary diagnosis of invasive adenocarcinoma of the colon and diagnosed between October 1, 1996 and June 30, 2000. Controls were randomly selected from North Carolina Division of Motor Vehicle lists if they were under 65 years of age, or from the Center for Medicare and Medicaid Services list if they were ≥65 years. Completed interviews were obtained from 701 African Americans (274 cases and 427 controls) and 957 whites (346 cases and 611 controls). Of those who were eligible, 84% of cases and 62% of controls were interviewed. The study was approved by the Institutional Review Board at the University of North Carolina School of Medicine and by equivalent committees at the collaborating hospitals.

Exposure Assessment. Questionnaires were administered in person in the participants' homes by specially trained registered nurses. The questionnaire collected information on lifestyle factors, such as physical activity and tobacco use; medical, family, and work histories; and use of over-the-counter medications. A 150-item food frequency questionnaire was used to measure usual dietary intake over the year before diagnosis for cases, or year before date of selection for controls (27). The questionnaire was modified to assess individual exposure to dietary carcinogens based on a meat cooking and doneness module developed by Sinha et al. (28). Details regarding the collection of dietary history and specifically HCA and PAH exposure have been previously documented (8). In brief, questions were added to assess 14 meat and fish items (i.e., hamburgers/cheeseburgers, beef steaks, pork chops/ham steaks, bacon, sausage, hot dogs, fried chicken, chicken/turkey, and fried fish/shellfish/fish sandwich) for frequency of intake, portion size (i.e., small, medium, or large), and cooking method. Color photographs were shown of each meat type (i.e., hamburger, steak, pork chop, bacon, and chicken/turkey) to facilitate reporting of cooking doneness. Meat intake frequency data, cooking method, and level of doneness were used to estimate values of three HCAs (MeIQx, PhIP, and DiMeIQx) and benzo(a)pyrene, using an exposure index that has been previously described in detail (28, 29).

Genotyping. Of the individuals with completed questionnaire data, 88% (93% of cases and 85% of controls) also agreed to provide a blood sample for DNA analyses. The 399 African Americans (197 cases and 202 controls) and 413 whites (203 cases and 210 controls) included for this analysis were based on all of the DNA samples available at the time this project was initiated and were selected in order of enrollment in the study.

We assessed whether there were differences between individuals who provided a blood sample and those who did not. Cases and controls who did not provide blood samples were more likely to be female ($P < 0.01$) and White ($P < 0.01$). There were no other significant differences (e.g., by age, education level, income, family history of colorectal cancer, smoking status, or total meat intake). In addition, there were no appreciable differences in the associations among meat intake, HCA exposure, and colon cancer, among cases and controls who provided blood samples, and the associations calculated among all cases and controls.

Genomic DNA was extracted from whole blood specimens using the PureGene DNA isolation kit (Gentra Systems, Inc., Minneapolis, MN). To determine *UGT1A7* genotype at position 129/131 and 208, two PCR-based assays were used to measure four alleles: *1 ($Asn^{129}Arg^{131}Trp^{208}$), *2 ($Lys^{129}Lys^{131}Trp^{208}$), *3 ($Lys^{129}Lys^{131}Arg^{208}$), and *4 ($Asn^{129}Arg^{131}Arg^{208}$). The Taqman assay was used to discriminate the polymorphisms at codons 129 and 131 (Applied Biosystems, Branchburg, NJ), as previously described (30). RFLP methods were used to discriminate the polymorphism at codon 208, as previously described (31).

The following quality control measures were employed. First, positive and negative controls were included in each PCR and Taqman experiment. Homozygote wild-type, heterozygote, and homozygote variants for each *UGT1A7* genotype from genomic DNA samples of known (via direct DNA sequencing) *UGT1A7* genotype were included. Second, repeated assays were conducted on five randomly selected samples from each experiment. There was 100% agreement. Third, five additional randomly selected samples were confirmed by direct DNA sequencing. Fourth, laboratory personnel were blinded to the case status of the samples.

Statistical Analysis. *UGT1A7* allele and genotype frequencies were calculated among African Americans and whites, cases and controls, separately. A χ^2 test was used to assess differences in allele frequencies between cases and controls. *UGT1A7* genotypes were categorized into the following imputed activity groups, based on the reduced HCA and PAH detoxification activity associated with the *UGT1A7*3* and *UGT1A7*4* alleles, as previously reported (19, 21): high (*1/*1, *1/*2, *2/*2), intermediate (*1/*3, *1/*4, *2/*3), and low (*3/*3, *3/*4, *4/*4). Observed *UGT1A7* genotype frequencies among controls were compared with expected genotype frequencies, calculated based on observed allele frequencies under the assumption of Hardy-Weinberg equilibrium (32). The Pearson χ^2 statistics (with degrees of freedom = number of alleles − 1) was used to test whether the expected number of individuals was significantly different from the observed number of individuals with each genotype, stratified by race.

All meat (by type, cooking method, and doneness preference), HCA (MeIQx, DiMeIQx, and PhIP), and benzo(a)pyrene variables were derived from food frequency questionnaire responses. The HCA and benzo(a)pyrene variables were derived by multiplying grams of meat intake (stratified by type, doneness, and method) by the compound concentration (ng/d) measured in that meat type. These variables were dichotomized, based on the median value (e.g., < and ≥ median) among controls. These variables have been previously described in detail (8).

For continuous covariates, tertile cut points were determined based on the distributions among all controls. These

covariates included intake of fruits, vegetables, dietary fiber, total fat, dietary folate, and total energy; physical activity, height, weight, and body mass index (kg/m^2). Fat intake was adjusted for total caloric intake using the residual method (33). Alcohol consumption was low in this population and therefore categorized as ever/never drank wine, beer, or liquor in the past year. Previously reported findings in this study population included an inverse association for dietary fiber (34) and no association with folate (35) or alcohol consumption (34) with risk of colon cancer.

Adjusted ORs and 95% CIs for colon cancer were calculated from unconditional logistic regression models (36). PROC LOGISTIC of the software package SAS (version 8.1; SAS Institute, Cary, NC) was used with the option in the MODEL statement to incorporate offsets, which takes into account the selection probabilities by age, race, and sex (25). Multivariable gene effects models included the following variables to adjust for potential confounding: race (African American and white), 5-year age groups (≤45, 46-50, . . ., ≥76 years), and sex. Multivariable joint effect models included the previously mentioned variables for race, age, and sex, in addition to dietary fiber, total fat, and total energy intake. Potential confounding was assessed by calculating the percent change observed in the ORs for various meat intake variables. The covariates included in the multivariable models resulted in a ≥10% difference in the ORs when added individually to the model. Covariates that were assessed but did not fulfill the criteria for confounding were mean daily folate intake (>276.6 and ≤276.6 μg), smoking (ever, never; current, former, never; current, formerly smoked for ≥36 years, formerly smoked for <36 years, never), mean body mass index (>28.5 and ≤28.5 kg/m^2), and alcohol intake in past year (ever, never beer, wine, or liquor).

Potential interaction or joint effects for *UGT1A7* genotype and meat-related exposures on risk of colon cancer were evaluated overall and separately among African Americans and whites. Interaction on the multiplicative scale was evaluated by the fit of an interaction term in the model, where $P < 0.10$ for the likelihood ratio test was interpreted as a statistically significant finding. Indicator variables were created to estimate the joint effects between dietary exposures and *UGT1A7*, where individuals with the lowest hypothesized associations, less than the median daily intake, and combined *UGT1A7* high/intermediate genotypes, comprised the common reference group (OR_{00}). These ORs were used to assess the expected joint effects for either additive ($OR_{10} + OR_{01} - OR_{00} > OR_{11}$) or multiplicative interaction ($OR_{10} \times OR_{01} > OR_{11}$), where OR_{10} was for high intake and *UGT1A7* high/intermediate genotype, OR_{01} was for low intake and *UGT1A7* low genotype, and OR_{11} was for their combined effects. Interaction contrast ratios (ICR) and 95% CIs were used to assess the magnitude and precision of the departure from additive joint effects, where ICR = ($OR_{11} - OR_{10} - OR_{01} + 1$; refs. 37, 38). For interpretation, an ICR > 0 implies joint effects are greater than additive (synergy), an ICR < 0 implies joint effects are less than additive (antagonism), and an ICR = 0 implies no departure from additivity.

Table 1. Demographic characteristics and daily dietary intake among colon cancer cases and population-based controls: The North Carolina Colon Cancer Study

	African Americans		Whites	
	Cases (n = 197)	Controls (n = 202)	Cases (n = 203)	Controls (n = 210)
Age				
Mean (SD)	62.6 (10.1)	65.6 (9.7)	65.6 (9.6)	65.6 (8.9)
Median (IQR)	64.0 (17.0)	68.0 (15.0)	67.0 (15.0)	67.0 (13.0)
Sex, *n*				
Men (%)	99 (50.3)	86 (42.6)	111 (54.7)	112 (53.3)
Women (%)	98 (49.7)	116 (57.4)	92 (45.3)	98 (46.7)
Total energy, kcal				
Mean (SD)	2,044.1 (942.0)	1,732.6 (825.4)	1,985.4 (786.3)	1,819.3 (654.0)
Median (IQR)	1,880.2 (1255.0)	1,522.8 (948.5)	1,873.7 (984.4)	1,734.1 (863.7)
Dietary fiber, g				
Mean (SD)	13.1 (6.3)	12.4 (5.6)	13.8 (5.3)	14.5 (5.8)
Median (IQR)	11.5 (7.2)	11.6 (5.5)	13.1 (6.6)	14.0 (7.8)
Dietary fat, g				
Mean (SD)	87.8 (43.3)	74.7 (38.5)	85.7 (42.5)	73.6 (32.6)
Median (IQR)	80.6 (58.6)	64.0 (45.3)	82.6 (52.4)	69.2 (41.9)
Total meat, g*				
Mean (SD)	128.3 (75.0)	110.7 (66.8)	115.3 (84.4)	103.9 (53.1)
Median (IQR)	114.1 (86.8)	101.2 (72.4)	93.9 (72.3)	97.2 (68.1)
Red meat, g†				
Mean (SD)	44.3 (36.2)	33.8 (28.6)	42.8 (39.7)	38.1 (30.9)
Median (IQR)	37.6 (43.7)	27.3 (31.7)	35.2 (36.4)	30.0 (34.7)
MeIQx, ng				
Mean (SD)	75.8 (66.3)	60.1 (67.3)	66.9 (69.6)	50.0 (55.0)
Median (IQR)	56.3 (78.5)	41.1 (59.4)	49.9 (70.1)	35.1 (57.7)
DiMeIQx, ng				
Mean (SD)	5.3 (5.1)	4.2 (5.7)	4.9 (6.2)	3.9 (4.7)
Median (IQR)	3.7 (6.2)	2.1 (4.6)	2.9 (5.4)	2.4 (5.2)
PhIP, ng				
Mean (SD)	86.7 (97.7)	88.5 (177.6)	103.8 (133.0)	83.7 (147.3)
Median (IQR)	58.5 (101.0)	29.9 (83.5)	65.7 (98.1)	48.3 (89.9)
BaP, ng				
Mean (SD)	18.0 (31.6)	17.4 (32.2)	41.4 (59.3)	38.2 (61.8)
Median (IQR)	6.1 (17.1)	4.6 (14.5)	15.9 (62.5)	17.0 (55.6)

NOTE: Study participants with UGT genotype data.
Abbreviations: IQR, interquartile range; BaP, benzo(a)pyrene.
*Total meat intake includes the following items: red meat, white meat, meat from spaghetti sauce, and beef stew.
†Red meat intake includes the following items: hamburger, steak, pork chop, sausage, and bacon.

Results

Characteristics of the study population are presented stratified by race in Table 1. In general, distribution of demographic and dietary characteristics was similar to what was previously reported for all North Carolina Colon Cancer Study participants (8). A summary of the differences observed among controls by race include a greater percentage of African Americans that had a lower level of education compared with whites, and there was a slightly greater percentage of ever smokers among whites than among African Americans (results not shown). For dietary factors, controls consumed less energy, similar fiber, and less fat compared with cases, regardless of race. The trend of greater total and red meat consumption among cases compared with controls was more apparent in African Americans than in whites. Median levels of intake were greater for all meat-related compounds among cases compared with controls, except for benzo(a)pyrene in whites. Among controls, MeIQx and PhIP were higher among African Americans, and benzo(a)pyrene was higher among whites. A detailed description of meat-related intake correlations in the entire North Carolina Colon Cancer Study population has been previously described (8). Briefly, among controls regardless of race, the strongest correlations for DiMeIQx, MeIQx, PhIP, and mutagenicity were with well/very well done red meat, and the strongest correlation for benzo(a)pyrene was with grilled/barbecued red meat (8).

Genotype and allele frequencies for *UGT1A7* among African Americans and whites are presented in Table 2. The *UGT1A7**3 allele and the *3/*3 genotype were less common among African-American controls compared with white controls. There were no differences in allele frequencies between cases and controls, regardless of race. The *2/*3 genotype frequency was slightly lower among white cases than controls, but genotype differences were not statistically significant. *UGT1A7* genotype frequencies were in Hardy-Weinberg equilibrium for African-American controls ($P = 0.571$) and white controls ($P = 0.113$).

When *UGT1A7* genotypes were grouped based on predicted activity assessed *in vitro* (21), we observed similar frequencies of the low-activity alleles (*3/*3, *3/*4, and *4/*4) among cases and controls for both African Americans (0.06 cases and 0.05 controls) and whites (0.17 cases and 0.17 controls). There was no association with colon cancer for *UGT1A7* low versus *UGT1A7* high or combined high/intermediate genotypes, overall or when assessed separately among African Americans or whites (Table 3).

Estimated joint effects between *UGT1A7* genotype and meat intake and cooked meat-derived HCA and benzo(a)pyrene exposure in relation to colon cancer are presented in Table 4, where the common reference group is individuals with less than the median dietary intake and *UGT1A7* high/intermediate genotype. *UGT1A7* modified the associations of several meat-related and colon cancer associations, although depending on the variable, the direction of interaction suggested either synergy or antagonism. For example, greater than additive joint effects were observed for UGT and well/very well done red meat and DiMeIQx, where ICRs were >0.5. For these factors, a moderate positive association was observed among individuals with the highest intake and *UGT1A7* low genotype, whereas null to weak associations were observed for meat/compound intake or genotype alone. Departure from interaction on the multiplicative scale was not statistically significant for UGT and well/very well done red meat (likelihood ratio test, $P = 0.707$) or DiMeIQx (likelihood ratio test, $P = 0.342$) on risk of colon cancer. Similar results were observed for UGT genotype and pan-fried meat. For PhIP, the ICRs were close to zero. Less than additive effects were observed for *UGT1A7* and red meat, grilled/barbecued red meat, and benzo(a)pyrene, where the ORs for genotype alone were greater than those for the joint effects and all three ICRs were <-0.5. The joint effects for UGT and meat-related factors differed by race only for DiMeIQx. However, because these ORs were imprecise, only results combining African Americans and whites are presented.

Discussion

Individual effects of *UGT1A7* genotype and joint effects with meat-related intake on the risk of colon cancer were estimated using data from a population-based, case-control study of African Americans and whites in North Carolina. No association was observed for *UGT1A7* genotype, comparing low to combined high and intermediate predicted activity groups, among African Americans or whites. Greater than additive joint effects were present for *UGT1A7* and well/very well done red meat and the HCA, DiMeIQx.

Our result for the individual effect of *UGT1A7* genotype does not support the previously reported positive association

Table 2. *UGT1A7* allele and genotype frequencies: The North Carolina Colon Cancer Study

UGT1A7	African Americans		Whites	
	Cases ($n = 197$)	Controls ($n = 202$)	Cases ($n = 203$)	Controls ($n = 210$)
Allele Frequency (n)*				
*1	0.37 (146)	0.37 (150)	0.35 (142)	0.31 (132)
*2	0.38 (149)	0.39 (158)	0.26 (106)	0.28 (119)
*3	0.25 (98)	0.24 (96)	0.39 (158)	0.40 (168)
*4	0.003 (1)	0 (0)	0 (0)	0.002 (1)
Fisher's exact test P		0.880		0.553
Genotype frequency (n)†				
*1/*1	0.12 (24)	0.12 (25)	0.13 (26)	0.12 (26)
*1/*2	0.30 (59)	0.30 (61)	0.18 (36)	0.14 (29)
*1/*3	0.20 (39)	0.19 (38)	0.27 (54)	0.24 (51)
*1/*4	0 (0)	0 (0)	0 (0)	0 (0)
*2/*2	0.14 (27)	0.15 (30)	0.09 (18)	0.10 (21)
*2/*3	0.18 (36)	0.19 (38)	0.17 (34)	0.23 (48)
*2/*4	0 (0)	0 (0)	0 (0)	0 (0)
*3/*3	0.06 (11)	0.05 (10)	0.17 (35)	0.16 (34)
*3/*4	0.01 (1)	0 (0)	0 (0)	0.01 (1)
*4/*4	0 (0)	0 (0)	0 (0)	0 (0)
χ^2 test P		0.974		0.628

*Allele frequency = number of alleles/number of chromosomes (n = number of chromosomes).
†Genotype frequency = number of participants with genotype/total number of participants (n = number of participants).

for the *UGT1A7*3* allele and colorectal cancer (19). However, the previous finding from a study by Strassburg et al. (19) may be a result of treatment-related selection bias. Irinotecan-based chemotherapy is a first-line treatment of advanced metastatic colorectal cancer, but toxicity in the form of severe neutropenia and diarrhea impede its use. Polymorphisms in the *UGT1A7* are thought to be responsible in part for increased toxicity (31), because of increased biotransformation of 7-ethyl-10-hydroxycamptothecin (SN-38), the pharmacologically active metabolite of irinotecan (39). It is possible that the prevalent cases available for participation in the previous study were more likely to have *UGT1A7* low-activity alleles, because they were more likely to have received more aggressive chemotherapy and survive long enough to be recruited. Genotype was not likely related to participant enrollment in the North Carolina Colon Cancer Study, because colon cancer cases were recruited within 6 months of diagnosis using a rapid ascertainment protocol (26).

We reported a slightly lower frequency of the *1 wild-type allele among White controls than the range (0.32-0.42) previously reported in German (19) and U.S. control groups (21, 30, 31) from either blood donor (21, 30) or clinic-based (19) populations. *UGT1A7*1* allele frequency among African-American controls was almost identical to the 0.38 frequency previously reported (30). Prevalence of the *UGT1A7* low-activity alleles among our population-based control group were similar to previous reports for the *4 allele among African Americans (30) and whites (19, 21) and for the *3 among African Americans (30). However, we observed a greater frequency for the *3 allele among whites compared with German (19) and U.S. control groups (21, 30). These previous studies were not population based, which may account for the differences seen in allelic prevalence.

We found contrasting patterns of interaction between types of meat and meat-related compound intake and *UGT1A7* genotype on risk of colon cancer. Greater than additive joint effects were present for *UGT1A7* and well/very well-done red meat and the HCA, DiMeIQx. Unexpectedly, there was a suggestion of antagonism between *UGT1A7* and grilled/barbecued red meat and the PAH, benzo(a)pyrene. The joint effects between meat intake or cooked meat–derived compound exposure and UGT polymorphisms have not been previously reported, although we had hypothesized that genotypes thought to confer less activity would increase the susceptibility for colon cancer among those with increased intake of HCAs and benzo(a)pyrene, and their surrogates, such as increased intake of well-done meat, or pan-fried meat. The similar effects for well/very well-done red meat and DiMeiQx and for grilled/barbecued red meat and benzo(a)pyrene are consistent with our previously reported finding for stronger correlations between individual HCAs and well-done meat, and for benzo(a)pyrene and grilled/barbecued red meat, than for other combinations (8). However, the contrasting direction of interaction remains difficult to explain, but it may reflect the variable degree of involvement of the glucuronidation pathway and more precisely, the UGT1A7 protein, in the *in vivo* metabolism of HCAs their *N*-hydroxylated metabolites and benzo(a)pyrene derivatives (21–23, 40, 41). For example, recent *in vitro* metabolic investigations showed that UGT1A7 plays a lesser role in the metabolism of *N*-OH-PhIP (42), that what was previously proposed (20). Instead, UGT1A1 may be the primary UGT involved in N-OH-PhIP glucuronidation (43). Another possible explanation for the contrasting joint effects is that the UGTs are differentially inducible by other dietary compounds, such as flavonoids (44, 45), which may effect expression of the individual isozymes.

Among individual HCAs, statistically joint effects were only present for DiMeIQx and UGT1A7. This was somewhat unexpected, because PhIP has the highest levels in cooked meat (5, 6, 46), and *N*-OH-PhIP has been documented as a good substrate for UGT1A7 (20). Despite overall levels, there is some evidence for greater carcinogen potential with DiMeIQx than with PhIP or MeIQx (47); however, both PhIP and MeIQx but not DiMeIQx have been documented as possible human carcinogens (2, 3). The possibility that the observed statistically significant joint effect for DiMeIQx and *UGT1A7* genotype may be due to chance given our small sample size, or due to multiple comparisons must be considered.

A limitation in our study was the retrospective assessment of diet. Cases may recall usual diet differently than controls, because of the effect of disease on dietary habits, resulting in biased ORs towards or away from the null (48). Bias due to disease-related changes in diet were of small concern, because total meat, red meat, and DiMeIQx levels did not significantly differ by stage of disease (results not shown), suggesting that if there were changes in diet following diagnosis, they were minimal.

Misclassification of gene effects may be an issue in these data, because genotype data was used to make assumptions about metabolic activity. We used the same categorization strategy of previous epidemiologic studies (30) for easier comparison. In addition, previous studies of UGT alleles and glucuronidation of benzo(a)pyrene derivatives and PhIP have indicated that the *3 and *4 alleles have the lowest activity (20, 21).

Another source of misclassification is that the effects observed may be independent of the *UGT1A7* genotype and linked to polymorphisms in other members of the UGT1A subfamily. Functional polymorphisms in UGT1A enzymes expressed in the liver and extrahepatic tissues that are involved in the *in vitro* metabolism of HCAs and benzo(a)pyrene have also been reported for UGT1A1 (42), UGT1A4 (49), UGT1A6 (50), UGT1A8 (51), UGT1A9 (31, 52), and UGT1A10 (53). The

Table 3. ORs for UGT1A7 genotype and colon cancer among all participants, African Americans and Whites: The North Carolina Colon Cancer Study

	Overall			African Americans			Whites		
	Cases (n = 400)	Controls (n = 412)	OR (95%CI)*	Cases (n = 197)	Controls (n = 202)	OR (95%CI)†	Cases (n = 203)	Controls (n = 210)	OR (95%CI)†
UGT1A7 genotype ‡									
High	190	192	1.0 (reference)	110	116	1.0 (reference)	80	76	1.0 (reference)
Intermediate	163	175	0.9 (0.7-1.3)	75	76	1.1 (0.7-1.7)	88	99	0.8 (0.5-1.3)
Low	47	45	1.1 (0.7-1.8)	12	10	1.2 (0.5-2.9)	35	35	1.0 (0.6-1.7)
Low versus high/ intermediate as reference group			1.1 (0.7-1.8)			1.1 (0.5-2.7)			1.1 (0.6-1.8)

*ORs are adjusted for age, race, sex, and offsets.
†ORs are adjusted for age, sex, and offsets.
‡ Individuals were categorized based on predicted UGT1A7 activity, where high = *1/*1, *1/*2, *2/*2; intermediate = *1/*3, *1/*4, *2/*3; and low = *3/*3, *3/*4, *4/*4. This analysis strategy was based on findings related to the *3 and *4 alleles (21) and to allow for comparison across other studies that use similar characterization.

Table 4. Main effects of meat-related intake and joint effects of meat-related intake and *UGT1A7* genotype on the association with colon cancer: The North Carolina Colon Cancer Study

	All participants		*UGT1A7*, high/intermediate		*UGT1A7*, low	
	Cases/controls	OR (95% CI)*	Cases/controls	OR (95% CI)*	Cases/controls	OR (95% CI)*
n	400/412		353/367		47/45	
Red meat (g/d)						
<29.3†	165/206	1.0 (reference)	139/182	1.0 (reference)	26/24	1.6 (0.9-3.1)
≥29.3	235/206	1.2 (0.9-1.7)	214/185	1.3 (0.9-1.9)	21/21	1.2 (0.6-2.5)
ICR (95% CI) = −0.7 (−2.0–0.6)						
Well/very well done red meat (g/d)						
<20.6†	156/206	1.0 (reference)	136/179	1.0 (reference)	20/27	1.1 (0.6-2.1)
≥20.6	244/206	1.4 (1.0-2.0)	217/188	1.4 (1.0-2.0)	27/18	2.0 (1.0-3.9)
ICR (95% CI) = 0.5 (−1.0–1.9)						
Pan-fried red meat (g/d)						
<9.9†	155/206	1.0 (reference)	133/179	1.0 (reference)	22/27	1.1 (0.6-2.2)
≥9.9	245/206	1.4 (1.0-1.9)	220/188	1.3 (0.9-1.9)	25/18	1.8 (0.9-3.6)
ICR (95% CI) = 0.3 (−1.0–1.7)						
Grilled/BBQ red meat (g/d)						
2.8†	195/204	1.0 (reference)	167/187	1.0 (reference)	28/17	2.4 (1.2-4.7)
≥2.8	205/208	0.9 (0.6-1.2)	186/180	1.0 (0.7-1.4)	19/28	0.7 (0.3-1.3)
ICR (95% CI) = −1.8 (−3.5–0.0)						
MeIQx (ng/d)						
<36.7†	147/206	1.0 (reference)	122/178	1.0 (reference)	25/28	1.3 (0.7-2.4)
≥36.7	253/206	0.9 (0.6-1.4)	231/189	0.9 (0.6-1.4)	22/17	1.2 (0.6-2.6)
ICR (95% CI) = −0.1 (−1.2–1.1)						
DiMeIQx (ng/d)						
<2.2†	137/204	1.0 (reference)	119/176	1.0 (reference)	18/28	1.0 (0.5-2.0)
≥2.2	263/208	1.6 (1.1-2.3)	234/191	1.5 (1.0-2.2)	29/17	2.4 (1.2-4.8)
ICR (95% CI) = 0.9 (−0.7–2.5)						
PhIP (ng/d)						
<39.1†	147/206	1.0 (reference)	124/178	1.0 (reference)	23/28	1.4 (0.7-2.6)
≥39.1	253/206	1.4 (1.0-1.9)	229/189	1.4 (1.0-2.0)	24/17	1.7 (0.9-3.5)
ICR (95% CI) = 0.2 (−1.2–1.5)						
BaP (ng/d)						
<6.4†	178/206	1.0 (reference)	154/185	1.0 (reference)	24/21	1.7 (0.9-3.3)
≥6.4	222/206	1.0 (0.7-1.4)	199/182	1.1 (0.8-1.5)	23/24	1.0 (0.5-1.9)
ICR (95% CI) = −0.6 (−1.8–0.6)						

Abbreviations: BaP, benzo(a)pyrene; BBQ, barbequed.

*The ORs for *UGT1A7* and meat groups were adjusted for age, race, sex, total meat, energy-adjusted fat intake, dietary fiber intake, total energy, and offsets. The ORs calculated for *UGT1A7* and the heterocyclic amines (MeIQx, DiMeIQx, PhIP) were adjusted for all heterocyclic amines, as well as age, race, sex, energy-adjusted fat intake, dietary fiber intake, total energy, and offsets. The OR calculated for BaP was adjusted for age, race, sex, energy-adjusted fat intake, dietary fiber intake, total energy, and offsets.

†Variable cut points are median values based on the distribution among controls.

entire UGT1 family is derived from a single gene locus (UGT1) which is composed of 17 exons (54). To synthesize the final protein, only one of 13 different exon 1 sequences on the locus is associated with four downstream exons, common to all UGT1A isoforms. It is expected that significant linkage disequilibrium exists between the *UGT1A7* polymorphisms and variants of other *UGT1A* genes relevant to the *in vivo* detoxification of HCAs and benzo(a)pyrene, because of the genomic structure of the *UGT1A* genes. For example, it has been shown that the variation at codon 208 of the *UGT1A7* gene is linked to the *UGT1A1*28* promoter variation (55), and this allele was also recently shown to modulate the glucuronidation of both N-OH-PhIP and benzo(a)pyrene derivatives in human livers (43, 56).[6] Therefore, it is possible that *UGT1A* genes other than *UGT1A7* are more biologically relevant in the metabolism of HCAs, such as *UGT1A1*.

Our findings do not support an increased risk of colon cancer due to polymorphisms in *UGT1A7*. However, our data do support possible joint effects between *UGT1A7* and dietary HCAs and benzo(a)pyrene on risk of colon cancer in a population-based case-control study. Our data also suggest that the metabolic genetic effects, such as those between *UGT1A7* and benzo(a)pyrene, may be more relevant at lower exposures, because at high levels the exposure is likely to saturate the enzyme activity and diminish the differences between ''high'' and ''low'' glucuronidation (57, 58). To the best of our knowledge, this is the first study to estimate joint effects between a UGT isozyme and dietary carcinogen exposure for colon cancer. In addition, the physiologic importance of UGT1A7 in colon tissue is unclear because expression of this isozyme has not been confirmed to be present in the colon in all studies (24, 59). The diversity of catalytic activity and substrate binding affinity of a number of additional UGT proteins involved in colon carcinogen detoxification and their expression found in colon tissue (10, 11, 59), may overshadow the effects of UGT1A7, especially in the colon. It may prove useful to further characterize individual isozymes for their etiologic relevance with colon cancer and as possible modifiers of the associations between dietary and environmental carcinogens, such as HCAs and PAHs.

[6] H. Girard et al. UDP-Glucuronosyltransferase 1A1 polymorphisms are important determinants of dietary carcinogen detoxification, in press.

Acknowledgments

We thank Michael Malfatti for his careful review and helpful comments during the preparation of this article.

References

1. Anonymous. Benzo[a]pyrene. IARC Monogr Eval Carcinog Risks Hum 1983;32:211–24.
2. Anonymous. PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine). IARC Monogr Eval Carcinog Risks Hum 1993;56:229–42.

3. Anonymous. MeIQx (2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline). IARC Monogr Eval Carcinog Risks Hum 1993;56:211–28.
4. Keating GA, Bogen KT. Methods for estimating heterocyclic amine concentrations in cooked meats in the US diet. Food Chem Toxicol 2001;39:29–43.
5. Sinha R, Knize MG, Salmon CP, et al. Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness. Food Chem Toxicol 1998;36:289–97.
6. Sinha R, Rothman N, Salmon CP, et al. Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings. Food Chem Toxicol 1998;36:279–87.
7. Lijinsky W. The formation and occurrence of polynuclear aromatic hydrocarbons associated with food. Mutat Res 1991;259:251–61.
8. Butler LM, Sinha R, Millikan RC, et al. Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. Am J Epidemiol 2003;157:434–45.
9. Mackenzie PI, Owens IS, Burchell B, et al. The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. Pharmacogenetics 1997;7:255–69.
10. Malfatti MA, Felton JS. *N*-glucuronidation of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and *N*-hydroxy-PhIP by specific human UDP-glucuronosyltransferases. Carcinogenesis 2001;22:1087–93.
11. Nowell SA, Massengill JS, Williams S, et al. Glucuronidation of 2-hydroxyamino-1-methyl-6-phenylimidazo[4, 5-b]pyridine by human microsomal UDP-glucuronosyltransferases: identification of specific UGT1A family isoforms involved. Carcinogenesis 1999;20:1107–14.
12. Styczynski PB, Blackmon RC, Groopman JD, Kensler TW. The direct glucuronidation of 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP) by human and rabbit liver microsomes. Chem Res Toxicol 1993;6:846–51.
13. Malfatti MA, Kulp KS, Knize MG, et al. The identification of [2-([14])C]2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine metabolites in humans. Carcinogenesis 1999;20:705–13.
14. Alexander J, Wallin H, Rossland OJ, et al. Formation of a glutathione conjugate and a semistable transportable glucuronide conjugate of N^2-oxidized species of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in rat liver. Carcinogenesis 1991;12:2239–45.
15. Kaderlik KR, Mulder GJ, Turesky RJ, et al. Glucuronidation of *N*-hydroxy heterocyclic amines by human and rat liver microsomes. Carcinogenesis 1994;15:1695–701.
16. King RS, Kadlubar FF, Turesky RJ. Food borne carcinogens: heterocyclic amines. Chichester (England): John Wiley and Sons, Ltd.; 2000.
17. Gschaidmeier H, Seidel A, Burchell B, Bock KW. Formation of mono- and diglucuronides and other glycosides of benzo(a)pyrene-3,6-quinol by V79 cell-expressed human phenol UDP-glucuronosyltransferases of the UGT1 gene complex. Biochem Pharmacol 1995;49:1601–6.
18. Kim PM, Wells PG. Genoprotection by UDP-glucuronosyltransferases in peroxidase-dependent, reactive oxygen species-mediated micronucleus initiation by the carcinogens 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and benzo[a]pyrene. Cancer Res 1996;56:1526–32.
19. Strassburg CP, Vogel A, Kneip S, Tukey RH, Manns MP. Polymorphisms of the human UDP-glucuronosyltransferase (UGT) 1A7 gene in colorectal cancer. Gut 2002;50:851–6.
20. Yueh MF, Nguyen N, Famourzadeh M, et al. The contribution of UDP-glucuronosyltransferase 1A9 on CYP1A2-mediated genotoxicity by aromatic and heterocyclic amines. Carcinogenesis 2001;22:943–50.
21. Guillemette C, Ritter JK, Auyeung DJ, Kessler FK, Housman DE. Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human UGT1A7 gene. Pharmacogenetics 2000;10:629–44.
22. Grove AD, Kessler FK, Metz RP, Ritter JK. Identification of a rat oltipraz-inducible UDP-glucuronosyltransferase (UGT1A7) with activity towards benzo(a)pyrene-7,8-dihydrodiol. J Biol Chem 1997;272:1621–7.
23. Zheng Z, Fang JL, Lazarus P. Glucuronidation: an important mechanism for detoxification of benzo[a]pyrene metabolites in aerodigestive tract tissues. Drug Metab Dispos 2002;30:397–403.
24. Basu NK, Kubota S, Meselhy MR, et al. Gastrointestinally distributed UDP-glucuronosyltransferase 1A10, which metabolizes estrogens and nonsteroidal anti-inflammatory drugs, depends upon phosphorylation. J Biol Chem 2004;279:28320–9.
25. Weinberg CR, Sandler DP. Randomized recruitment in case-control studies. Am J Epidemiol 1991;134:421–32.
26. Aldrich TE, Vann D, Moorman PG, Newman B. Rapid reporting of cancer incidence in a population-based study of breast cancer: one constructive use of a central cancer registry. Breast Cancer Res Treat 1995;35:61–4.
27. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.
28. Sinha R, Rothman N. Exposure assessment of heterocyclic amines (HCAs) in epidemiologic studies. Mutat Res 1997;376:195–202.
29. Kazerouni N, Sinha R, Hsu CH, Greenberg A, Rothman N. Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study. Food Chem Toxicol 2001;39:423–36.
30. Zheng Z, Park JY, Guillemette C, Schantz SP, Lazarus P. Tobacco carcinogen-detoxifying enzyme UGT1A7 and its association with orolaryngeal cancer risk. J Natl Cancer Inst 2001;93:1411–8.
31. Villeneuve L, Girard H, Fortier L-C, Gagne JF, Guillemette C. Novel functional polymorphisms in the UGT1A7 and UGT1A9 glucuronidating enzymes in Caucasian and African-American subjects and their impact on the metabolism of 7-ethyl-10-hydroxycamptothecin and flavopiridol anti cancer drugs. J Pharmacol Exp Ther 2003;307:117–28.
32. Cavalli-Sforza LL, Bodmer WF. The genetics of human populations. San Francisco: W. H. Freeman; 1971.
33. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
34. Satia-Abouta J, Galanko JA, Potter JD, Ammerman A, Martin CF, Sandler RS. Associations of total energy and macronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina colon cancer study. Am J Epidemiol 2003;158:951–62.
35. Satia-Abouta J, Galanko JA, Martin CF, Potter JD, Ammerman A, Sandler RS. Associations of micronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina Colon Cancer Study. Cancer Epidemiol Biomarkers Prev 2003;12:747–54.
36. Breslow N, Day N. Statistical methods in cancer research: the analysis of case-control studies. Lyon: IARC; 1980.
37. Assmann SF, Hosmer DW, Lemeshow S, Mundt KA. Confidence intervals for measures of interaction. Epidemiology 1996;7:286–90.
38. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology 1992;3:452–6.
39. Iqbal S, Lenz HJ. Determinants of prognosis and response to therapy in colorectal cancer. Curr Oncol Rep 2001;3:102–8.
40. Strassburg CP, Nguyen N, Manns MP, Tukey RH. UDP-glucuronosyltransferase activity in human liver and colon. Gastroenterology 1999;116:149–60.
41. Fang JL, Beland FA, Doerge DR, et al. Characterization of benzo(a)pyrene-*trans*-7,8-dihydrodiol glucuronidation by human tissue microsomes and overexpressed UDP-glucuronosyltransferase enzymes. Cancer Res 2002; 62:1978–86.
42. Girard H, Thibaudeau J, Court MH, Fortier LC, Villeneuve L, Guillemette C. UGT1A1 promoter polymorphism as an important determinant of heterocyclic amine detoxification. In: Vancouver: ISSX; 2004.
43. Malfatti MA, Felton JS. Human UDP-glucuronosyltransferase 1A1 is the primary enzyme responsible for the *N*-glucuronidation of *N*-hydroxy-PhIP *in vitro*. Chem Res Toxicol 2004;17:1137–44.
44. Sugatani J, Yamakawa K, Tonda E, et al. The induction of human UDP-glucuronosyltransferase 1A1 mediated through a distal enhancer module by flavonoids and xenobiotics. Biochem Pharmacol 2004;67:989–1000.
45. van der Logt EM, Roelofs HM, Nagengast FM, Peters WH. Induction of rat hepatic and intestinal UDP-glucuronosyltransferases by naturally occurring dietary anticarcinogens. Carcinogenesis 2003;24:1651–6.
46. Sinha R, Rothman N, Brown ED, et al. High concentrations of the carcinogen 2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine (PhIP) occur in chicken but are dependent on the cooking method. Cancer Res 1995;55:4516–9.
47. Layton DW, Bogen KT, Knize MG, Hatch FT, Johnson VM, Felton JS. Cancer risk of heterocyclic amines in cooked foods: an analysis and implications for research. Carcinogenesis 1995;16:39–52.
48. Dosemeci M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am J Epidemiol 1990;132:746–8.
49. Ehmer U, Vogel A, Schutte JK, Krone B, Manns MP, Strassburg CP. Variation of hepatic glucuronidation: novel functional polymorphisms of the UDP-glucuronosyltransferase UGT1A4. Hepatology 2004;39:970–7.
50. Ciotti M, Marrone A, Potter C, Owens IS. Genetic polymorphism in the human UGT1A6 (planar phenol) UDP-glucuronosyltransferase: pharmacological implications. Pharmacogenetics 1997;7:485–95.
51. Huang YH, Galijatovic A, Nguyen N, et al. Identification and functional characterization of UDP-glucuronosyltransferases UGT1A8*1, UGT1A8*2 and UGT1A8*3. Pharmacogenetics 2002;12:287–97.
52. Girard H, Court MH, Bernard O, et al. Identification of common polymorphisms in the promoter of the UGT1A9 gene: evidence that UGT1A9 protein and activity levels are strongly genetically controlled in the liver. Pharmacogenetics 2004;14:501–15.
53. Elahi A, Bendaly J, Zheng Z, et al. Detection of UGT1A10 polymorphisms and their association with orolaryngeal carcinoma risk. Cancer 2003;98:872–80.
54. Gong QH, Cho JW, Huang T, et al. Thirteen UDPglucuronosyltransferase genes are encoded at the human UGT1 gene complex locus. Pharmacogenetics 2001;11:357–68.
55. Kohle C, Mohrle B, Munzel PA, et al. Frequent co-occurrence of the TATA box mutation associated with Gilbert's syndrome (UGT1A1*28) with other polymorphisms of the UDP-glucuronosyltransferase-1 locus (UGT1A6*2 and UGT1A7*3) in Caucasians and Egyptians. Biochem Pharmacol 2003;65:1521–7.
56. Fang JL, Lazarus P. Correlation between the UDP-glucuronosyltransferase (UGT1A1) TATAA box polymorphism and carcinogen detoxification phenotype: significantly decreased glucuronidating activity against benzo(a)pyrene-7,8-dihydrodiol(−) in liver microsomes from subjects with the UGT1A1*28 variant. Cancer Epidemiol Biomarkers Prev 2004;13:102–9.
57. Vineis P, Bartsch H, Caporaso N, et al. Genetically based *N*-acetyltransferase metabolic polymorphism and low-level environmental exposure to carcinogens. Nature 1994;369:154–6.
58. Vineis P, Martone T. Genetic-environmental interactions and low-level exposure to carcinogens. Epidemiology 1995;6:455–7.
59. Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. Annu Rev Pharmacol Toxicol 2000; 40:581–616.